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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LAM, ANN Y	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,345	ARKHAMMAR ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 7, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/04, 4/12/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The claimed invention is directed to non-statutory subject matter. A data set as set forth in claim 20 is not a statutory class of invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 2, it is not clear as to what the term "influence" means (it is not defined in the specification.)

As to claims 17-19 since claim 1 is not a screening assay, it is not clear how the method of claim 1 is used as a screening program. Moreover, claims 18 and 19 do not even recite any additional method steps.

Claim 19, line 3, recites the limitation "as defined herein". It is unclear as to where Applicant is referring which provides the definition of biologically toxic substance. For example, is Applicant referring to the specification? If so, where in the specification? Or is Applicant referring to claim 19 itself, and if so, where?

Claim 20 is a product claim, but depends from claim 1, a method claim, and thus it is unclear as to what the product comprises. Moreover, Claim 20 does not include a transitional phrase such as "comprising", and thus it is unclear what is included in the body of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1-5, 8-11, 13-15, 17, 18, 20-23, 26, 27 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Miesenbock et al., 6,670,449.

As to claims 1, 21, 22, 31, Miesenbock discloses a method for detecting translocation of a component fused to a luminophore (green fluorescent protein, column 4, lines 6-62, and column 14, lines 37) in a cell in mechanically intact or permeabilized living cells (column 22, line 28), the method comprising:

detecting translocation of light emitted from said luminophore (column 3, lines 53-64), wherein

said component is part of an intracellular pathway (col. 18, lines 23-24, and 33-35), the intracellular pathway involving an enzymatic reaction (i.e., tyrosine kinase, col. 18, lines 34-35),

said translocation is detected by measuring changes in luminescence intensity (column 14, lines 6-8, 14-18, lines 26-29),

said luminophore is encoded by and expressed from a nucleic acid sequence in said cell (column 11, lines 49-50 and column 12, lines 36-38), and

said translocation is from membrane to cytoplasm (e.g. internalization of tyrosine kinases and G protein-coupled receptors, column 18, lines 33-35.)

As to claim 2, the translocation is caused by an influence (i.e., any influence that causes internalization of tyrosine kinases and G protein-coupled receptors in column 5, lines 38-41; or due to effects of drugs, see column 18, lines 8-17).

As to claim 3, the influence comprises contact between the mechanically intact or permeabilised living cells and a chemical substance and/or incubation of the cells with a chemical substance (e.g. incubation with a drug, column 18, lines 8-17.)

As to claim 4, the cells comprise a group of cells contained within a spatial limitation type (column 5, lines 36-41.)

As to claim 5, the cells comprises multiple groups of cells contained within multiple spatial limitations (column 5, lines 36-41.)

As to claim 8, the translocation results in quenching of fluorescence, the quenching being measure as a decrease in the intensity of the fluorescence (column 18, line 13.)

As to claim 9, the translocation results in energy transfer, the energy transfer being measure as a change in the intensity of the luminescence (column 14, lines 14-18, and 25-30; and column 18, lines 35-37.)

As to claim 10, the intensity of the light is a function of the luminescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response, (column 18, lines 10-14.)

As to claim 11, the light to be measured passes through a filter which selects the desired component of the light to be measured and rejects other components (column 32, lines 22-23, column 33, line 8.)

As to claims 13, 26, the luminophore is a luminescent or fluorescent polypeptide (column 4, lines 61-62.)

As to claims 15, 27, the cells are selected from the group consisting of fungal cells, invertebrate cells, vertebrate cells (column 5, line 49.)

As to claim 14, the fluorescence comes from a fluorophore encoded by and expressed from a nucleotide sequence harboured in the cells (column 11, lines 49-50, column 12, lines 36-47.)

As to claim 17, the method is used as a screening program (column 18, lines 8-17.)

As to claim 18, the method is for screening program for the identification of a biologically active substance that directly or indirectly affects an intracellular signaling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signaling pathway (i.e., the method is for drug screening, column 18, lines 8-17.)

As to claim 20, a set of data obtained by the above method is disclosed (column 18, lines 8-17.)

As to claim 23, the fluorescent polypeptide is a Green Fluorescent Protein (column 4, lines 61-62.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 16 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miesenbock et al., 6,670,449.

Miesenbock discloses the invention substantially as claimed (see above), except for the step of incubation at the specifically claimed temperature.

However it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233. Miesenbock discloses the general conditions of the claims (as described above.) The temperature ranges as claimed are the optimum or workable ranges, and thus discovering the optimum or workable temperature ranges requires only routine skill in the art as dictated by *In re Aller*.

5. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miesenbock et al., 6,670,449, in view of Zarling et al., 5,674,698.

Miesenbock discloses the invention substantially as claimed (see above with respect to claim 1; see also claim 5.) Miesenbock specifically teaches that the experiments are performed in vitro (see for example col. 32, lines 58-59.)

However, Miesenbock does not disclose that the spatial limitations are arranged in one or more arrays on a common carrier type, and that the spatial limitations are wells in a plate of micro-titer type.

Zarling also discloses an assay method for detecting intensity of light emitted from labels provided in intact viable cells (column 5, lines 9-14; and column 5, lines 66 – column 6, line 1).

As to claim 6, Zarling further discloses that the cells are contained within spatial limitations that are arranged in one or more arrays on a common carrier type (see column 23, lines63-64 and column 37, line 28.)

As to claim 7, the spatial limitations are wells in a plate of micro-titer type (see column 39, lines 10-32.)

It would have been obvious to provide in the Miesenbock method an array of wells in a plate of micro-titer type as taught by Zarling as a well known mechanism used to contain cells in an assay, as disclosed by Zarling.

6. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miesenbock et al., 6,670,449, in view of Schlessinger et al., 5,889,150.

Miesenbock discloses the invention substantially as claimed (see above with respect to claim 17 and 1.) Moreover, Miesenbock teaches that the method can be used to diagnose disorders involving alterations of exocytosis (col. 18, lines 6-8.) Miesenbock also discloses use of the method to determine the effects of drugs on exocytotic process for example (column 18, lines 9-10.) Miesenbock discloses that the method can be used for screening for compounds affecting trafficking processes of medical relevance (column 18, lines 30-31), and specifically teaches that the intracellular signaling pathway involving tyrosine kinases is an example of transport pathways that can be monitored using the disclosed method (col. 18, lines 33-35.)

However, Miesenbock does not teach that the screening program is for the identification of toxic substances that exert its toxic effect by interfering with an

intracellular signaling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the translocation of the fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signaling pathway.

Schlessinger teaches that it is desirable to understand the regulation of cell growth and oncogenesis by providing the ability to identify target proteins for tyrosine kinases, including both receptor and cytoplasmic tyrosine kinases (col. 2, lines 55-59.) Schlessinger teaches methods, compounds and compositions to provide the means to gain that understanding (col. 11, line 66 – col. 12, line 4.)

Schlessinger also teaches that the assay can be used to identify compounds that interfere with the interaction between the binding partners, wherein the assay involves preparing a reaction mixture containing activated tyrosine kinase protein and the disclosed adaptor protein (col. 29, lines 26-31.) The disclosed assay to identify compounds that interfere with the interaction in the Schlessinger assay is considered the same as an assay to identify toxic substances that exert its toxic effect by interfering with an intracellular signaling pathway (as claimed by Applicant). The signaling pathway in this case involves tyrosine kinase.

Schlessinger also discloses that the detection step in the assay can be accomplished using any of a variety of other immunoassays or detectably labeled peptide probes (col. 13, lines 5-8.)

It would have been obvious to one of ordinary skill in the art to provide an assay to identify the interfering compounds as taught by Schlessinger using the Miesenbock

method of analysis since Schlessinger teaches that it is desirable to understand the regulation of cell growth and oncogenesis by providing the ability to identify target proteins for tyrosine kinases, including both receptor and cytoplasmic tyrosine kinases, and that any variety of assay methods can be used such as using detectably labeled peptide probes.

7. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miesenbock et al., 6,670,449, in view of Tsien et al., 5,912,137.

Miesenbock discloses the invention substantially as claimed (see above with respect to claims 23, 14, 13 and 1.)

Moreover Miesenbock discloses that the invention also includes mutants of green fluorescent protein which exhibit environment sensitive excitation and/or emission spectra and are useful, for example, as reporter moieties in the hybrid molecules of the invention (column 4, lines 61-65.)

Tsien also teaches use of green fluorescent proteins as reporter moieties in assays, and further teaches that the green fluorescent protein with a F64L mutation allows it to be more fluorescent (col. 11, lines 37-38, and line 43.)

It would have been obvious to one of ordinary skill in the art to use the green fluorescent protein with a F64L mutation as taught by Tsien as the mutant green fluorescent protein in the Miesenbock method in order to allow it to be more fluorescent,

as taught by Miesenbock, as would be desirable for more easily obtaining experimental results.

Response to Arguments

Applicant's arguments filed July 7, 2004 have been fully considered but they are not persuasive.

Applicant argues on pages 15 to 16 that Miesenbock is concerned with measuring cell trafficking, as opposed to measuring localization of intracellular components, that is components of an intracellular pathway.

Applicant argues on page 16 that Miesenbock does not concern measuring localization of intracellular components, involving an enzymatic reaction, as is claimed by the present invention. Applicant points to Applicant's specification on page 28, lines 14-21 to refer to what Applicant means by 'enzymatic reaction'.

The specification on page 28, lines 14-21 specifically gives examples of protein kinases as enzymes in involved in the method.

Miesenbock discloses this element by teaching that examples of transport pathways monitored in the assay include those involving internalization of activated signaling receptors such as tyrosine kinases (col. 18, lines 33-35.) An assay to monitor internalization of tyrosine kinase or phospholipase is an assay of an intracellular pathway involving enzymatic reaction (as defined by Applicant on page 28, line 18.) In addition, Miesenbock specifically teaches that the disclosed method is anticipated to be

applicable to detecting the release of vesicular contents within a cell (col. 3, lines 62-64.)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.L.

Christopher L. Chin

CHRISTOPHER L. CHIN
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9/30/04